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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,816	08/26/2003	Nicholas Van Bruggen	11669.0113USC1	5367

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
10/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/648,816	VAN BRUGGEN ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-21 and 30-46* is/are pending in the application.

4a) Of the above claim(s) *7-10 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,11-14,19-21 and 30-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed 7/27/07 is acknowledged. Claims 45 and 46 were added.

2. Claims 1, 3-21 and 30-46 are pending. Claims 7-10, and 15-18, drawn to non-elected inventions, are with withdrawn from consideration.

Claims 1, 3-6, 11-14, 19-21, and 30-46 are examined on the merits.

Claim Objections/Rejections Withdrawn:

Claim Rejections - 35 USC § 112

3. The rejection of claim 31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants' persuasive arguments.

4. The rejection of claims 41 and 44 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendments to the claims.

5. The rejection of claims 1, 6, 30, 31, 36-44 under 35 U.S.C. 112, first paragraph, for lack of enablement of the full scope of the claimed methods is withdrawn upon further consideration.

Claim Rejections - 35 USC § 103

6. The rejection of claims 1, 6, 14-21, 30-38, 42 and 43 under 35 U.S.C. 103(a) as being unpatentable over Ferrara (supra) in view of Bates (Bates, D.O. et al. Am. J. Physiol. 271: H2520-H2528, 1996) and further in view of Aiello (U.S. 6,114,320; issued Sep. 5, 2000; effective filing May 1, 1996) or Ozaki (Ozaki, H. et al. Exp. Eye Res. 64: 505-517, 1997; cited in IDS) is withdrawn upon further consideration.

Claims Rejections Maintained and New Grounds of Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46 is indefinite because the phrase "the monitering" lacks antecedent basis in claim 43, from which it depends.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3-5, 11-13, 39 and 40 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ferrara (WO 94/10202; published 11 May 1994; cited in the IDS).

Claim 1 has been amended to recite that the mammal is administered an effective amount of a hVEGF antagonist to reduce CNS edema.

Applicants state that they do not agree with the rejection of record because the disclosure in an asserted anticipating reference must provide an enabling disclosure of the claimed subject matter, and that applicants believe that Ferrara does not enable the treatment of CNS edema with a hVEGF antagonist. Further, applicants state that, as presented in the declaration of Dr. Van Bruggen (previously submitted for parent application 09/218,481), it was unknown if the inhibition of VEGF by an antagonist would be sufficient to inhibit cerebral edema in vivo; that contradictory evidence of the role of VEGF in cerebral edema existed n the literature at the time of the invention; and that previous studies correlating peritumoral edema formation with increase levels of mRNA expression in tumor cells, while suggesting a role for VEGF in edema, presented no evidence of direct causation. Therefore, applicants assert, Ferrara does not anticipate the claims because the reference does not enable the treatment of CNS edema with a hVEGF antagonist.

Applicants' arguments have been carefully considered, but fail to persuade because the claims include within their scope methods of treating patients having neoplastic disease such as a brain tumor, and Ferrara clearly teaches that hVEGF antagonists would be useful in the treatment of patients with having undesirable vascular permeability, such as edema associated with a brain tumor. Thus, the patient population of Ferrara is within the scope of the patient population of the present claims and the active steps are the same as that of Ferrara. Because Ferrara clearly

teaches treatment of a population of patients having cerebral edema, Ferrara therefore teaches the step of administering an effective amount of an hVEGF antagonist to reduce cerebral edema in a patient with a brain tumor. Therefore, the rejection is maintained for the reasons of record.

9. Claims 1-6, 11-14, 19-21, 30-40, 42, 43, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara (supra) in view of Kovacs (Kovacs, Z. et al., Stroke, 27: 1865-1873, 1996; cited in the IDS), in view of Cheng (Cheng, S.-Y. et al., Proc. Natl. Acad. Sci., USA, 94: 12081-12087, 1997), in view of Ullrich (US 6,177,401; issued Jan. 23, 2001; effective filing date Feb. 9, 1994), and further in view of Zhao (Zhao, L. et al., Journal of Cardiovascular Pharmacology, 32(1): 1-4, 1998, July).

The claimed inventions include within their scope methods of treating cerebral edema, or stroke, where the cerebral edema is due to a non-neoplastic condition such as stroke or head injury, which may be ischemic stroke.

Ferrara teaches methods of treatment comprising administering hVEGF antagonists, where the hVEGF antagonist may be a hVEGF receptor fusion protein (see page 22, lines 10-33; claim 28; page 2, line 29-page 3, line 4). Ferrara also teaches combination therapy (see page 17, lines 15-28). Furthermore, it appears that Ferrara appreciated that hVEGF antagonists would be useful in the treatment of diseases or disorders characterized by undesirable vascular permeability, such as edema associated with a brain tumor. Ferrara teaches that that appropriate dosage of antagonist will depend on the type of disease and also, among other factors, the response to the antagonist (see page 16, lines 19-24). Thus, in a treatment for CNS edema, it appears that the mammal would be monitored for a reduction in a symptom of CNS edema, such

as a decrease in intracranial pressure. Ferrara teaches methods of treating diseases or disorders associated with edema, but fails to specifically identify disorders such as the non-neoplastic condition of stroke or head injury.

Kovacs teaches that in ischemic brain VEGF is present in macrophages, neurons, and glial cells; and that VEGF receptor flt is induced in endothelial cells along with the progression of angiogenesis with brain infarct in a middle cerebral artery occlusion model in rats (see abstract). Thus, Kovacs associates VEGF protein levels and VEGF receptor protein levels with ischemic stroke.

Cheng teaches that overexpresion of either VEGF121 or VEGF165 causes reproducible and predictable intracerebral hemorrhage (see page 12081, 2nd column). Thus, Cheng associates VEGF activity with hemorrhagic stroke.

Ullrich teaches that inhibition of VEGF signaling in implanted C6 glioblastoma cells in nude mice resulted in a reduction in tumor-induces edema formation (see column 27, line 20 – column 28, line 30). Thus, Ullrich associates VEGF inhibition with a reduction in edema.

Zhao teaches that VPF (VEGF) causes a rapid increase in the blood brain barrier (BBB) permeability in culture capillary endothelial cells from the bovine brain. Thus, Zhao associates VEGF with an increase in the permeability of brain blood vessels.

Thus, the prior art provides evidence that one of skill in the art would have been aware that VEGF plays an active role in the increase in blood vessel leakiness (or blood vessel permeability) in the brain because Kovacs shows that VEGF and its receptor are present in the ischemic brain; because Cheng teaches that it plays a role in the development of hemorrhagic stroke; because Ullrich finds that tumor associated edema is decreased when VEGF signaling is

inhibited; and because Zhao teaches that the blood vessels of the brain respond to VEGF by increasing permeability. Since edema is caused by an increase in blood vessel permeability, and in particular brain blood vessels respond to increases in VEGF to become more permeable, there appears to be evidence in the prior art that VEGF was a causative agent in the occurrence of brain edema. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods and antagonists of Ferrara for the treatment of central nervous system edema that was associated with either a brain tumor, or associated with a non-neoplastic condition because VEGF appears to cause an increase in blood vessel permeability in the brain, which leads to the occurrence of edema.

10. Claims 1-6, 11-14, 19-21, 30-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara (supra) in view of Kovacs (Kovacs, Z. et al., Stroke, 27: 1865-1873, 1996; cited in the IDS), in view of Cheng (Cheng, S.-Y. et al., Proc. Natl. Acad. Sci., USA, 94: 12081-12087, 1997), in view of Ullrich (US 6,177,401; issued Jan. 23, 2001; effective filing date Feb. 9, 1994), and further in view of Zhao (Zhao, L. et al., Journal of Cardiovascular Pharmacology, 32(1): 1-4, 1998, July).

Included within the scope of the claims are methods where the antagonist is administered at within about four days after identification of the presence of cerebral edema.

The cited references teach as set forth above, and do not teach a specific time for administering an hVEGF antagonist. However, the timing of the administration appears to fall within the scope of optimizing the administration of a drug through routine experimentation, which is considered within the skill of one of ordinary skill in the art.

See MPEP 2144.05: A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
October 15, 2007

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER